Citation:

Erkkila AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr.* 2004 Sep; 80(3): 626-632

PubMed ID: 15321802

Study Design:

Cohort study.

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the relation between fish consumption and the progression of angiographically defined coronary atherosclerosis in a group of post-menopausal women undergoing baseline and three-year follow-up coronary angiography as part of a randomized clinical trial of hormone replacement therapy (HRT).

Inclusion Criteria:

- Post-menopausal women
- Coronary stenoses of 30% or greater of the luminal diameter.

Exclusion Criteria:

None described.

Description of Study Protocol:

Recruitment

Participants of the Estrogen Replacement and Atherosclerosis trial.

Design

Randomized, double-blind, placebo-controlled trial.

Blinding Used

Participants to the hormone therapy and operators of the angiography to the women's dietary habits

and temporal sequence of the films.

Intervention

Hormone replacement of 0.625mg conjugated equine estrogen, 0.625mg conjugated equine estrogen, or placebo.

Statistical Analysis

The normality of continuous variables was checked, and log transformations were applied as needed. Differences in baseline characteristics and nutrient intakes were tested between the different intake categories by using independent-samples T-tests, Wilcoxon's rank-sum test or chi-square test, as appropriate. The association between total fish intake and different types of fish intake was tested by using the test parameters of changes in mean minimum coronary artery diameter and mean percentage stenosis with the use of mixed-model analysis of covariance (ANCOVA). These measurements were adjusted for age, the location of the coronary segment, the time of follow-up, study clinic, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, race, body mass index (BMI), smoking, use of cholesterol-lowering medication, HRT, diabetes and energy intake (model 1). Model 2 included adjustments for the factors in model 1 and energy-adjusted intakes of saturated, monounsaturated and polyunsaturated fats, cholesterol, fiber and alcohol. Further adjustments for blood pressure; serum concentrations of total cholesterol, HDL, LDL, triacylglycerol and inflammatory markers; education and strenuous physical activity were also made. Differences in the development of new lesions were tested with ANCOVA. Spearman correlation coefficients adjusted for BMI were calculated between inflammatory markers and fish intake. A value of $P<0.05$ (two-tailed) was considered statistically significant.

Data Collection Summary:

Timing of Measurements

- Dietary intake during the year before baseline measurements
- Quantitative coronary angiography at baseline and at 3.2±0.6 years.

Dependent Variables

Quantitative coronary angiography using standardized techniques. Review and analysis of the paired films was done using validated cine projectors. The reference, minimum and average luminal diameters and degree of stenosis (as a percentage of the reference diameter) were assessed in proximal epicardial segments. Development of a new lesion was defined as the presence of one or more segments with less than 15% stenosis at baseline and an increase of 15 or more percentage points at follow-up.

Independent Variables

Dietary intake by a validated, semiquantitative, 126-item food-frequency questionnaire. Energy intakes less than 660kcal and more than 3,500kcal per day or more than 11 food items left blank were excluded. Frequency of fish consumption was calculated by summing the frequency of intake of tuna, dark fish or other fish. Intake of tuna and dark fish were also summed alone to determine long-chain n-3 fatty acid intake.

Description of Actual Data Sample:

- *Initial N:* 229 females
- *Attrition (final N):* 229
- *Age:* 65.0±6.7 for less than two servings of fish a week and 64.4±6.9 for two or more servings of fish a week
- *Ethnicity:* 85% white, 12% African American and 3% other in the less than two servings a week group and 83%, 12% and 5%, respectively, in group eating two or more servings of fish a week
- *Other relevant demographics:* Those with less than two servings of fish a week had a lower educational level
- *Anthropometrics:* Those with less than two servings of fish a week had less strenuous physical activity
- *Location:* Finland, Boston and North Carolina.

Summary of Results:

Findings

HRT did not affect the progression of atherosclerosis.

There was no difference in the baseline values for serum lipids, inflammatory markers and blood pressure. Those with two or more servings of fish a week had higher intakes of energy, protein, cholesterol, alcohol and carotene and lower intakes of carbohydrates.

Among the 42% of the women who were diabetic, change in minimum coronary artery diameter was significantly smaller in women who eat two or more servings of fish a week (P=0.02). Mean baseline percentage stenosis was also greater in this group and there was a smaller change ($P \leq 0.001$).

Women who ate two or more servings of fish a week had significantly fewer new lesions (P= 0.02).

Women who ate one or more servings of tuna or dark fish a week had a smaller change in minimum coronary artery diameter (P=0.02). This association was diminished and limited to diabetic women when adjusted for the factors in model 1. The association became significant when adjusted for the factors in model 2, which suggests an independent effect of tuna and dark fish (P= 0.02). Among diabetic women, baseline stenosis was greater and changes in percentage stenosis were smaller (models 1 and 2) in those who ate one or more servings of tuna and dark-meat fish a week.

Mean baseline minimum coronary artery diameter was smaller and percentage stenosis was greater in the diabetic women who ate one or more servings of "other fish" than those who had lower intakes. In the nondiabetic women, those reporting more than one serving of "other fish" a week had smaller changes in minimum coronary artery diameter and percentage stenosis. There were fewer segments with new lesions in women who consumed one or more servings of "other fish" a week.

Fish intake was inversely correlated with concentrations of vascular adhesion molecule 1 (VAM-1) but there were no correlations with C-reactive protein (CRP), IL-6 and ICAM-1.

Author Conclusion:

Fish consumption was associated with a significantly reduced progression of coronary atherosclerosis in post-menopausal women with coronary artery disease (CAD). This relation was strongest in diabetic women.

Reviewer Comments:

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes

3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A

6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes

	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes